Kidney International, Vol. 68, Supplement 98 (2005), pp. S69–S75

Early detection and prevention of diabetic nephropathy: A challenge calling for mandatory action for Mexico and the developing world

RICARDO CORREA-ROTTER and LUIS GONZÁLEZ-MICHACA

Department of Nephrology and Mineral Metabolism Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico

Early detection and prevention of diabetic nephropathy: A challenge calling for mandatory action for Mexico and the developing world. During the last decades, developing countries have experienced an epidemiologic transition characterized by a reduction of infectious diseases and an increase of chronic degenerative diseases. This situation is generating tormenting public health, financial, and social consequences. Of particular relevance is type 2 diabetes mellitus and its chronic complications, particularly cardiovascular disease and diabetic nephropathy, because mortality of the patient with diabetes is, in most instances, related to these complications.

There is a clear need to implement diagnostic and treatment strategies to reduce risk factors for development of diabetes (primary prevention), to detect risk factors of chronic complications in early stages of diabetes (secondary prevention), and to prevent further progression of those that already have renal injury (tertiary prevention). Microalbuminuria is an early marker of renal injury in diabetes, and its early detection can help the timely use of renal preventive measures, which would avoid the extremely high costs of renal replacement treatment for end-stage renal disease as well as that of other cardiovascular complications.

Preventive strategies are of very little or no impact, if the primary physician has limited knowledge about the natural history of diabetic nephropathy, the beneficial effect of early preventive maneuvers for delaying its progression, and the social and economic impact of end-stage renal disease. It is therefore imperative to assure in our health systems that general practitioners have the ability and commitment to detect early diabetes complications, in order to promote actions that support regression or retard highly morbid cardiovascular and renal conditions.

DEMOGRAPHIC AND EPIDEMIOLOGIC TRANSITION

During the second half of the last century, the world experienced highly significant demographic and epidemiologic changes, some of which have positively influenced life expectancy and the public health scenario in most nations. Some of the most important changes worth mentioning are: major improvements of general sanitation procedures, the development of specific public health interventions, and the advent of specific medical therapies including vaccination and antibiotics. This improvement in life expectancy has conditioned major global demographic changes, with those observed in developing nations being particularly significant.

While incidence of infectious diseases has been consistently declining, chronic diseases have become the main cause of morbidity and mortality in most of the emerging world, a trend initiated decades before in developed countries. Figure 1 shows mortality causes in Mexico in 1940 as compared with those in the year 2000; these data clearly support the previous statement. Parallel to the increase in life expectancy, there has been a worldwide declination of fertility and birth rates with consequent increase in the mean age of populations; this being more pronounced in the developing world [1, 2]. The increased length of human life is a consequence of a combination of several factors including: reduction of malnourishment, advances in medical practice and technology, in particular those related to communicable and perinatal diseases, urbanization, education initiatives, development of public health programs and, as previously mentioned, the implementation of adequate sanitation practices [3]. In Mexico, one of the major achievements during the last century was indeed reduction in mortality. Life expectancy of Mexicans has risen more than double in less than 7 decades, increasing from a mean of 36 years in 1930 to 75 years in 2000 [4]. The National Population Council of Mexico has estimated the change in the shape of the population pyramid from its actual status (Fig. 2A) to a significantly different change in 2005 (Fig. 2B), in which the actual high number of young people under 20 years of age will be substituted by a much older population [5].

These demographic changes are linked to an epidemiologic transition characterized by a reduction of

Key words: prevention, diabetic nephropathy, CME, primary physicians, Mexico, developing nations.

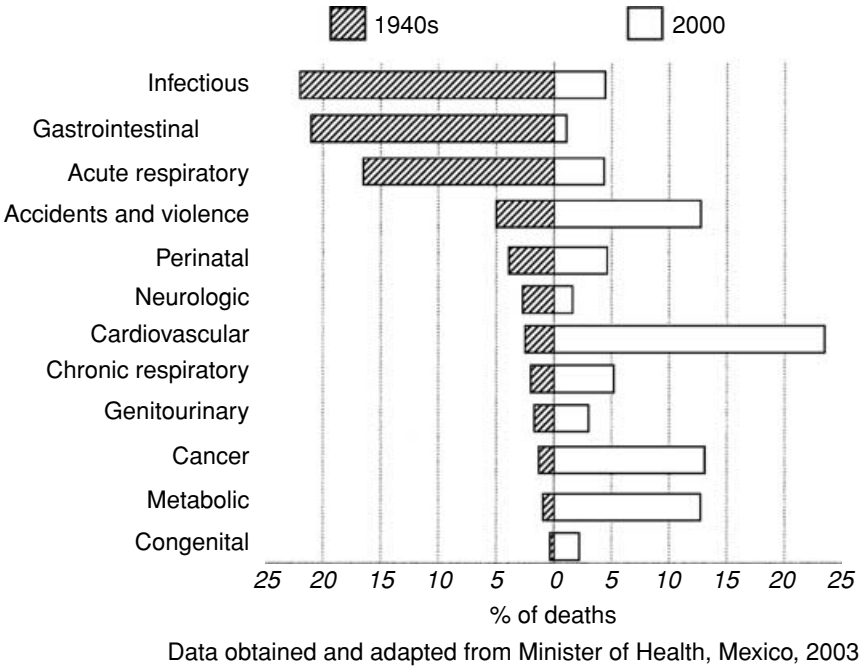

Fig. 1. Mortality causes in Mexico in 1940 compared with those from the year 2000. Predominance of infectious causes has shifted to chronic degenerative diseases.

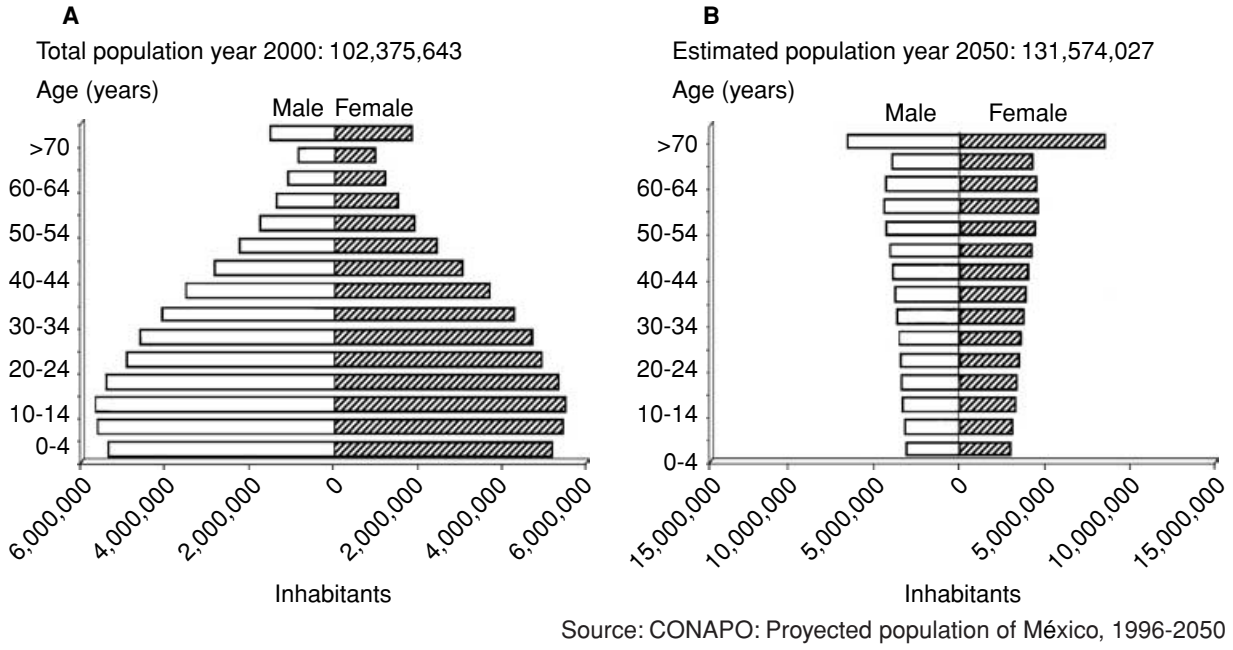

Fig. 2. (*A*) Population pyramid of Mexico for the year 2000. Data obtained from the 2000 National Census. (*B*) Estimation of the shape of the population pyramid of Mexico for the year 2005. Data calculated by the National Population Council of Mexico.

communicable infectious diseases and an increase in the incidence and prevalence of chronic degenerative non-communicable diseases. This complex and continuous evolving process has modified the scenario and required an urgent modification of health policies. Of particular relevance is the change of the burden of disease usually present in younger groups to the adult population, particularly the elderly. Additionally, the disease processes in infectious illnesses, which were usually short and evolved either to cure or death, have changed to what is observed in chronic diseases, which is usually longstanding and may require continuous medical care and treatment for years or even decades [1, 2, 6, 7].

In addition, other demographic phenomena have contributed to a shift to the current complex scenario, in which chronic maladies predominate as responsible for a high percentage of the health budget of the developing world. Industrialization and development have favored

the migration of extensive rural populations to urban and suburban areas. Accelerated urbanization has been characterized in the emerging world by the appearance of extensive areas of irregular settlements located in the outskirts of major cities, which lack adequate urban sanitary and general services and medical care facilities. Two of the most relevant features of the marginality in which these suburban communities develop are extensive poverty and lack of access to medical care.

Massive industrialization and development have favored almost universal changes in lifestyle and dietary habits, with a predominance of some unhealthy ones such as sedentary life, high fat and high carbohydrate diets, high sodium consumption, and smoking, among others. Highly developed and industrialized nations have been able to progressively establish some educational and regulatory strategies to counterbalance the commercial forces that promote these unhealthy habits, therefore conditioning a loss of consumers and advocates. In contrast, poorer nations have become the target of advertising and promotion of corporations that visualize these regions of the world as unregulated, uneducated, and highly attractive markets for consumption of unhealthy products such as the ones previously mentioned. For example, during the last couple of decades, tobacco smoking has become significantly higher in the underdeveloped world, a situation that has been accompanied by aggressive and poorly regulated advertising. This factor has imposed an additional burden on the health system of societies, which already have extremely high growth rates of chronic pathologic conditions such as cardiovascular diseases, diabetes mellitus, obesity, chronic renal diseases, or cancer; these conditions are negatively impacted by such dietary and lifestyle habits [6–12].

The continuous increase in metabolic, cardiovascular, and neoplastic chronic diseases is already generating devastating public health and financial and social consequences in most emerging nations that cannot cope with the cost burden of technology-driven medical interventions and drugs needed to treat these diseases. To make matters worse, the near future foresees a continued increase in the incidence of these diseases as a consequence of increased life expectancy, and this is particularly true for Mexico. It is therefore clear that preventive strategies may play a central role in modifying the expected public health scenario, given the actual trends of increase of chronic diseases.

Growth of type 2 diabetes mellitus

Of particular relevance among chronic degenerative diseases and major contributors to excess morbidity and mortality present in Mexico are non-insulin–dependent or type 2 diabetes mellitus and its chronic complications, particularly cardiovascular disease and diabetic nephropathy.

Mortality of the patient with diabetes is, in most instances, related to cardiovascular and renal complications that require costly medical procedures and which may impose an even larger financial burden to the system [13]. Indeed, type 2 diabetes mellitus may well be the largest health problem we face in Mexico during the 21st century. This is similar to what is happening in most other latitudes of the planet, yet to a larger extent, given the very high prevalence of the disease and its complications [12]. Growth of type 2 diabetes mellitus prevalence is expected to happen worldwide; nevertheless, developed nations such as those in the European Union or the United States are expecting an increase between 40% and 70% in the next 30 years, whereas growth in developing areas of the world, including Mexico, will be around 250% in the same period of time.

Worldwide, Mexico has one of the most elevated type 2 diabetes mellitus prevalence. This survey shows a general prevalence of around 25% in the general population between 25 and 40 years of age [14]. The Mexican Survey of Chronic Diseases, performed in 1993, showed a general prevalence in the total Mexican population of 8.2% of type 2 diabetes mellitus and, in addition, almost one third of those diagnosed with the disease did not know they had it [15]. These high numbers are related to genetic predisposition [16, 17], in conjunction with increased life expectancy and the changes in human behavior and lifestyle that occurred in our country over the last century, which is associated with the demographic and epidemiologic transition discussed above [4, 18]. Type 2 diabetes mellitus has, in the last century, become a major cause of mortality in the Mexican population as well as the first cause of premature disability. Figure 3 shows the mortality related to diabetes mellitus in Mexico during the 8 eight decades. It is clear that the trend is moving to a continuous increase in mortality due to this disease; in 1992, the mortality rate was of 2.5 $\times$ 100,000 inhabitants, and for the year 1997 it was 15 times higher [18]. The Minister of Health of Mexico recently stated that this trend is expected to continue; deaths from diabetes frequently linked to obesity are increasing by 3% each year, and diabetes mellitus itself has become Mexico's leading cause of death, representing 12% of total deaths in the country [19].

Prevention of diabetes complications

The International Society of Nephrology held, in March 2004 at the Bellagio Study and Conference Center of the Rockefeller Foundation, a highly relevant workshop devoted to the discussion of strategies and actions directed toward the prevention of renal diseases in the emerging world. Discussion was focused mainly on

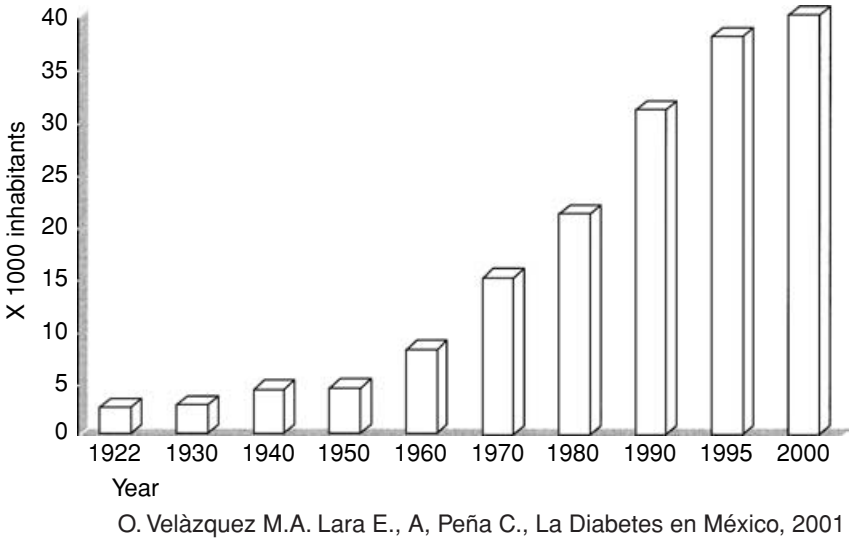

Fig. 3. Mortality related to diabetes mellitus in Mexico during the last decades. Adapted from [18].

pathogenetic issues associated with vascular injury, diabetes mellitus, and hypertension, epidemiologic analysis of different worldwide scenarios, and discussion of the burden of these diseases in the emerging world. In addition, early detection and preventive strategies that have been implemented, and other potentially useful ones, were discussed. The conference concluded that the actual trend of permanent increase in the incidence of diabetes mellitus and associated renal disease requiring renal replacement therapy is imposing a financial burden that cannot be met by most nations of the world. There is an urgent need for specific strategies and programs for early detection and prevention of vascular and renal complications of diabetes mellitus to avert the global threat of an uncontrolled pandemic.

End-stage renal disease has indeed become a major health threat for the whole world, yet the steeper increase in its incidence and prevalence is happening in the developing world [2–5]. Over 1 million individuals who develop end-stage renal disease every year require expensive renal replacement therapy (dialysis or kidney transplantation). Non-insulin–dependent diabetes mellitus is by far the major contributor to this increase in end-stage renal disease.

Worldwide, the increased prevalence of diabetes mellitus has expanded the premature mortality associated with disease due to a higher frequency of its complications [20, 21]. There is a clear need to implement diagnostic and treatment strategies to reduce those risk factors for the development of diabetes (primary prevention), to detect in early stages in patients that already have diabetes and are at risk of developing chronic complications (secondary prevention), and to prevent further progression of those that already have renal injury (tertiary prevention) [22]. We are also required to strongly promote an increase in the knowledge of risk factors as well as preventive measures in the general public, primary care physicians, government officials, and policy makers.

The presence of urinary albumin excretion in patients with diabetes has been clearly identified as a risk indicator for nephropathy, cardiovascular injury, and death [22–24]. Microalbuminuria is one of the earliest markers of microvascular disease in the patient with diabetes, and it is widely accepted that it precludes development of overt albuminuria (>300 mg/day) and progressive renal functional deterioration. Microalbuminuria may also be associated with insulin resistance syndrome, and it is sometimes associated with conditions such as obesity and hypertension [25].

Medical procedures developed for preventing diabetic nephropathy must be viewed as limited in their effectiveness, because the exact pathogenic factors responsible for this condition are unknown. Some strategies that may slow the progression of renal disease include the maintenance of good glycemic control [26–28] and blood pressure control, the limiting of protein intake [29–31], changes in lifestyle including smoking cessation, prompt treatment of urinary tract infections, and the avoidance of potentially nephrotoxic drugs and radiographic dyes [32].

Since the last decade, it has been well established that intensive control of blood glucose can prevent retinal, renal, and neuropathic complications of type 1 and 2 diabetes. The Diabetes Control and Complications Trial [28] and the United Kingdom Prospective Diabetes Study [33] were the first of several studies that established the value of intensive control of blood glucose. Establishment of intensive glucose control has demonstrated a reduction in albuminuria (surrogate end point) and a prevention or retardation in the development of diabetic nephropathy leading to end-stage renal disease (actual end point) [34, 35].

Diabetic renal disease is accompanied by the development of hypertension in almost all patients, and it is well known that antihypertensive treatment delays progressive renal injury [36]. Several studies have demonstrated that the blockade of the renin-angiotensin system (RAAS) with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers is of additional benefit. RAAS-blocking agents administered either in early or later stages of the disease may induce a beneficial effect in terms of reduction of microalbuminuria and subsequent reduction of progressive renal injury [36–41]. The pathophysiologic participation of the RAAS in renal injury of diabetic renal disease, and the subsequent implementation of pharmacologic interventions to block this system, have modified our ability to treat the patient with diabetes with nephropathy. It is clear that the beneficial renoprotective effect of the RAAS blockade is, in part, independent of the antihypertensive mechanism and may induce reduction or regression of microalbuminuria in early states of renal injury, even in the absence of hypertension.

The fact that microalbuminuria is an early marker of renal injury has allowed its application as a monitoring instrument of early stages of the disease [25, 31, 35, 37], and the timely identification of diabetics that can benefit from the renal protective effects of blockade of the RAAS system and other preventive measures. Given the extremely high costs of renal replacement treatment for end-stage renal disease as well as that of other cardiovascular complications, it is clear that this procedure may be highly cost-effective and an invaluable aid to mitigate the very large financial burden of treating end-stage renal disease. It may also favor better patient outcomes in countries of the developing world [29–31, 34]. Actually, we believe that this approach may be the way of the future, in terms of control of an epidemic growth of diabetes mellitus, diabetic nephropathy, and other chronic vascular diseases.

It is clear that preventive actions must be implemented as early as possible in the evolution of diabetes; however, multiple situations have precluded timely actions. Some of the most relevant are the absence of overt symptoms in most patients, lack of health-related education of the general population, lack of knowledge of primary care physicians about the importance of preventive measures, lack of commitment by the medical community, delayed referral to nephrologists and, of course, scarce resources for preventive medicine from national health systems [42]. Development and execution of successful preventive programs require joint efforts that include the participation of patients and their relatives, physicians and other health workers, national government agencies, the pharmaceutical industry, and international agencies. Of utmost importance is to raise awareness and to educate the general public, patients, policymakers, and primary physicians in charge of patients on the importance of generating changes in lifestyle conditions that may reduce the risk of development of chronic conditions, and on those simple maneuvers directed to early detection of risk factors. In parallel with educational efforts, we need effective programs geared toward early detection of risk factors. Blood glucose and systemic blood pressure monitoring play a key role in this issue. In addition, periodic determination of microalbuminuria is of particular importance, given its known value as an indicator of progressive renal and vascular disease. Once early stages of renal disease are diagnosed, simple procedures need to be put in place, again emphasizing lifestyle changes (reduction in sodium intake and other dietary indications) and early pharmacologic interventions that should include RAAS blockade and possibly other drugs such as low-dose aspirin or statins, if hyperlipidemia is present [43].

Validation of an educational program for primary physicians

In spite of the availability of clear opportunities for intervention at almost any stage of diabetic nephropathy, preventive strategies are of very little or no impact, if the primary physician who is the first medical contact of the general community has limited knowledge about the natural history of diabetic nephropathy, the beneficial effect of early preventive maneuvers for delaying its progression, and the social or economic impact of end-stage renal disease. It is therefore imperative to assure in our health systems that general practitioners and family physicians have the ability and commitment to detect early manifestations of diabetes mellitus complications, and to promote the prescription of lifestyle changes and medication that favor regression or retard highly morbid cardiovascular and renal conditions. In addition, continued professional development for health care is an important tool for health improvement of communities, and it is considered as a means to maintain high standards of care as well as of improvement on recruiting, motivating, and retaining high quality staff [44].

Although the process needed to create infrastructure and local educational programs has to be planned from the inside of each country considering special needs and characteristics of the society where it will be implemented, global assistance, when possible, may be highly supportive. This may assure greater success and a higher retention of health workers and physicians in the programs.

There is scarce information related to the implementation and results of continuous medical education programs directed to first-contact physicians and aimed to modify knowledge and prescription practices of primary and secondary prevention of diabetic kidney disease. In Mexico, we are conducting a research and educational

project directed to first-contact physicians and aimed at primary and secondary prevention of diabetic kidney disease. We believe that programs of this nature may lead to a reduction of the growth in the number of diabetic end-stage renal diseases requiring renal replacement therapy, and therefore may lead to a decrease in associated mortality. The project includes the development, validation, and establishment of an educational program in the public health sector at the national level oriented to train general practitioners and family physicians in the knowledge of basic pathophysiology, natural history and, specifically, on prevention and treatment strategies for early complications of diabetes mellitus, with emphasis on diabetic nephropathy. In addition, we have specifically designed instruments for this purpose, in order to evaluate participants' knowledge at the moment of the program's initiation and its impact on the acquisition of knowledge and the short and midterm modification of diagnostic and therapeutic attitudes directed to reduction of progression of renal injury. Finally, another objective is to generate increased awareness, motivation, and self assurance on the importance of primary care physicians' intervention for national public health purposes.

This project has been developed by a group of nephrologists, in conjunction with other professionals (epidemiologist, sociologist, and teaching professionals), and includes oral presentations, written documents, posters with algorithms, as well as directed case discussions. Once developed, it will be applied and validated by means of an experimental study, in which selected health centers will be randomly chosen to participate as experimental or control centers. Physicians from control health centers will receive standard educational and information opportunities, yet no specific, directed intervention will be provided to physicians of experimental centers. Both will be evaluated and monitored in the same form, so that the results can be compared. The capacity to modify diagnostics and therapeutic attitudes in the educative program will be measured by evaluation of participant physicians before and after receiving the qualification on diabetic nephropathy, and comparing these results with practices of physicians from control centers (patient questionnaires exploring medical indications and recommendations at 6 months after implementation of the program, and patient chart comparisons on indications and prescriptions after the educational maneuver at 6 months after the program is concluded). This is a nationwide program to be implemented initially by 30 collaborating nephrologists, educators, and health promoters (educators and coinvestigators), who will be carefully trained in a standardized, educational program that is to be provided to 600 general practitioners. Based on the obtained results, a proposal will be developed to implement a permanent national program of education in diabetic nephropathy and other microvascular complications of this disease, and to generate the Mexican guidelines for primary and secondary prevention of diabetic kidney disease. Funding and support for this initiative have been obtained from Mexican government agencies (National Council for Science and Technology) and from the pharmaceutical industry. Success in obtaining the goals of the project is of utmost importance to provide additional evidence of the benefit of investing on education to promote prevention of chronic diseases.

CONCLUSION

Action for control of chronic complications of diabetes mellitus requires immediate attention that cannot be delayed because this could prove to be extremely costly for emerging nations. An adequate policy implies, among other strategies, the initiation of extensive educational strategies, extrapolating knowledge previously obtained elsewhere with simultaneous development of local initiatives that may allow us to better understand and face local conditions.

Reprint requests to Ricardo Correa-Rotter, M.D., Head, Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, Tlalpan 14000, Mexico, DF Mexico.
E-mail: correarotter@prodigy.net.mx

REFERENCES

1. Omran AR: The epidemiologic transition: A key of the epidemiology of population change. *Milibank Mem Fund Q* 49:509–538, 1971
2. Reddy KS, Yusuf SL: Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 97:596–601, 1998
3. World Bank: *World Development Report: Investing in Health*, New York, Oxford University Press, 1993
4. Rivera JA, Barquera S, Campirano F, Tovar V, *et al*: Epidemiological and nutritional transition in Mexico: Rapid increase of non-communicable chronic diseases and obesity. *Public Health Nutr* 5:113–122, 2002
5. Partida Bush V: *Proyecciones de la población económicamente activa, de la matrícula educativa de los hogares y las viviendas y de la población por tamaño de la localidad*, México, Consejo Nacional de Población, 1999, pp 17–19, Available at: http://www.conapo.gob.mx/publicaciones/Proyecciones/pdf/proypea.pdf, Accessed 2003
6. Murray CJL, Lopez AD: *Global Comparative Assessments in the Health Sector*, Geneva, Switzerland, World Health Organization, 1994
7. Pearson TA, Jamison DT, Tergo-Gauderies J: Cardiovascular disease, in *Disease Control Priorities in Developing Countries*, edited by Jamison DT, Mosley WH, New York, Oxford University Press, 1993 pp 577–599
8. Peto R, Lopez AD, Boreham J, *et al*: Mortality from smoking worldwide. *Br Med Bull* 52:12–21, 1996
9. World Health Organization: *Tobacco or Health? First Global Status Report*, Geneva, Switzerland, World Health Organization, 1996
10. Popkin BM: The nutrition transition in low-income countries: An emerging crisis. *Nutr Rev* 52:285–298, 1994
11. Lang T: The public health impact of globalization of food trade, in *Diet, Nutrition and Chronic Disease: Lessons from Contrasting Worlds*, edited by Shetty PS, McPherson K, Chichester, United Kingdom, Wiley, 1997, pp 173–187
12. Drewnowski A, Popkin BM: The nutrition transition: New trends in the global diet. *Nutr Rev* 55:31–43, 1997

13. Whelton PK, Brancati FL, Appel LJ, Klag MJ: The challenge of hypertension and atherosclerotic cardiovascular disease in economically developing countries. *High Blood Press* 4:36–45, 1995
14. Encuesta Nacional de Enfermedades Crónicas 2000: *Dirección General de Epidemiología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán*, México, D.F, Secretaría de Salud, 2000
15. Encuesta Nacional de Enfermedades Crónicas 1993: *Dirección General de Epidemiología, Instituto Nacional de la Nutrición*, México, D.F., Secretaría de Salud, 1993
16. Gill-Randall R, Adams D, Lewis M, *et al*: Type 2 diabetes mellitus—Genes or intrauterine environment? An embryo transfer paradigm in rats. *Diabetologia* 47:1354–1359, 2004
17. Baier LJ, Hanson RL: Genetic studies of the etiology of type 2 diabetes in Pima Indians: Hunting for pieces to a complicated puzzle. *Diabetes* 53:1181–1186, 2004
18. Velázquez O, Lara-Esqueda A, Peña A: La Diabetes en México, in Boletín Epidemiológico en Español, Panamerican Health Organization. 8, 1999, pp 2
19. Reuters AlertNet: Diabetes now Mexico's leading cause of death. Report from the Mexican Minister of Health, available at: www.alertnet.org/thenews/newsdesk/N24404782.htm, Reuters, accessed August 24, 2004
20. Zimmet P: Globalization, coca-colonization and the chronic disease epidemic: Can the doomsday scenario be averted? *J Intern Med* 247:301–310, 2000
21. Songer T: The economic costs of NIDDM. *Diabetes Metabol Rev* 8:389–404, 1992
22. Parving H-H: Diabetic nephropathy: Prevention and treatment. *Kidney Int* 60:2041–2055, 2001
23. King H, Aubert RE, Herman WH: Global burden of diabetes 1995–2025, prevalence, numerical estimates, and projections. *Diabetes Care* 21:1414–1431, 1998
24. Viberti G: The need for tighter control of cardiovascular risk factors in diabetic patients. *J Hypertens* 21(Suppl 1):S3–6, 2003
25. Lane JT: Microalbuminuria as a marker of cardiovascular and renal risk in type 2 diabetes mellitus. A temporal perspective. *Am J Physiol Renal* 286:F442–50, 2004
26. Ravid M, Brosh D, Ravid-Safran D, *et al*: Main risk factors for nephropathy in type 2 DM are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch Intern Med* 158:998–1004, 1998
27. The Diabetes Control and Complications Trial (DCCT): Design and methodologic considerations for the feasibility phase. The DCCT Research Group. *Diabetes* 35:530–545, 1986
28. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. *Kidney Int* 47:1703–1720, 1995
29. Praga M: Slowing the progression of renal failure. *Kidney Int* 61(Suppl 80):18–22, 2002
30. Waugh NR, Robertson AM: Protein restriction for diabetic renal disease. *Cochrane Database Syst Rev* (2):CD002181, 2000
31. Pijls LT, de Vries H, Donker AJ, van Eijk JT: The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: A randomized trial. *Nephrol Dial Transplant* 14:1445–1453, 1999
32. Fassi A, Sangalli F, Colombi F, *et al*: Beneficial effects of calcium channel blockade on acute glomerular hemodynamic changes induced by cyclosporine. *Am J Kidney Dis* 33:267–275, 1999
33. United Kingdom Prospective Diabetes Study Group (UKPDS): Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
34. Coresh J, Astor B, Sarnak MJ: Evidence for increased cardiovascular risk in patients with chronic kidney disease. *Curr Op Nephrol Hypertens* 13:73–81, 2004
35. MacIsaac RJ, Jerums G, Cooper ME: New insights into the significance of microalbuminuria. *Curr Opin Nephrol Hypertens* 13:83–91, 2004
36. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 329:1456–1462, 1993
37. Yuyun MF, Khaw KT, Luben R, *et al*: Microabuminuria independently predicts all-cause and cardiovascular mortality in British population: The European Prospectiva Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *Int J Epidem* 33:189–198, 2004
38. Brenner BM, de Zeeuw D, Parving HH, *et al*: RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
39. Lewis EJ, Berl T, Raz I, *et al*, for the collaborative Study Group: Renoprotective effects of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
40. Hostetter TH: Prevention of end-stage renal disease due to type 2 diabetes. *N Engl J Med* 345:910–912, 2001
41. Heart Outcomes Prevention Evaluation (HOPE) Study: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253–259, 2000
42. Lameire N, Wauters JP, Gorriz Teruel JL, *et al*: An update on the referral pattern of patients with end-stage renal disease. *Kidney Int* 61:S27–S34, 2002
43. Gæde P, Vedel P, Larsen N, *et al*: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348:383–393, 2003
44. Brown CA, Belfield CR, Field SJ: Cost effectiveness of continuing professional development in health care: A critical review of the evidence. *BMJ* 324:652–655, 2002